



## Fluticasone furoate/umeclidinium/vilanterol (Trelegy® Ellipta®)

### New Drug Update

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October 2017

<b>Drug Name:</b>	fluticasone furoate/umeclidinium/vilanterol
<b>Trade Name (Manufacturer):</b>	Trelegy Ellipta (GlaxoSmithKline)
<b>Form:</b>	Inhalation powder in 2 foil blister strips (1 containing fluticasone furoate, 1 containing umeclidinium/vilanterol) per dose; 30 blister strips per inhaler
<b>Strength:</b>	100 mcg/62.5 mcg/25 mcg
<b>FDA Approval:</b>	September 18, 2017
<b>Market Availability:</b>	Currently available
<b>FDA Approval Classification:</b>	Standard Review
<b>Classification:</b>	Specific Therapeutic Class (HIC3): Beta-adrenergic-Anticholinergic-Glucocorticoid, Inhaled (B64)

### INDICATION<sup>1</sup>

Trelegy Ellipta is indicated for the long-term, once-daily, maintenance treatment of patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema, who are on a fixed-dose combination of fluticasone furoate and vilanterol for airflow obstruction and reducing exacerbations in whom additional treatment of airflow obstruction is desired or for patients who are already receiving umeclidinium and a fixed-dose combination of fluticasone furoate and vilanterol. It is not indicated for the relief of acute bronchospasm or the treatment of asthma.

Trelegy Ellipta is a combination of fluticasone furoate (an inhaled corticosteroid [ICS]), umeclidinium (an anticholinergic), and vilanterol (a long-acting beta<sub>2</sub>-adrenergic agonist [LABA]).

### CONTRAINDICATIONS/WARNINGS

Use of Trelegy Ellipta is contraindicated in those with severe hypersensitivity to milk proteins or any ingredients (active or excipients). Hypersensitivity reactions, including anaphylaxis, angioedema, rash, and urticaria may occur; discontinue Trelegy Ellipta if a hypersensitivity reaction occurs. Paradoxical bronchospasm has been reported with inhaled medications. If this occurs, the patient should be treated with a short-acting bronchodilator and Trelegy Ellipta should be discontinued.

Trelegy Ellipta contains a boxed warning for asthma-related death, as LABAs can increase this risk.

Trelegy Ellipta should not be used in patients with rapidly deteriorating, potentially life-threatening episodes, or for the relief of acute symptoms. It should not be used at doses higher than recommended or in combination with other medications containing a LABA, due to the risk of excessive inhaled sympathomimetic drugs.

As symptoms of a COPD exacerbation may resemble symptoms of pneumonia, patients and prescribers should be vigilant in monitoring for pneumonia. Likewise, Trelegy Ellipta contains medications that can suppress the immune system, making users more susceptible to infections and the infections may be of a greater severity. Trelegy Ellipta should be used with caution, if at all, in patients with tuberculosis infections; ocular herpes simplex; or systemic fungal, bacterial, viral, or parasitic infections.

ICS medications, such as fluticasone furoate, may cause localized *Candida albicans* infections of the mouth and pharynx. Should an infection occur, it should be treated with appropriate local or systemic antifungal therapy while continuing Trelegy Ellipta. Rinsing the mouth following administration can help reduce this risk. While ICS agents can be systemically active, effects on the hypothalamic-pituitary-adrenal (HPA) axis were not observed with therapeutic doses of Trelegy Ellipta; however, this may occur at higher than recommended doses or in combination with a strong cytochrome P450 3A4 (CYP3A4) inhibitor. Patients converted from systemic to inhaled corticosteroids should be monitored cautiously due to the risk of adrenal insufficiency, particularly in those on  $\geq 20$  mg/day prednisone (or equivalent). Several months may be required for HPA function recovery and precautions, including patient instruction for management, should be taken during recovery. ICS agents may cause a decrease in bone mineral density; BMD assessment is recommended prior to initiation and periodically thereafter.

Glaucoma, increased intraocular pressure, and cataracts have been reported with inhaled anticholinergics and corticosteroids. Monitoring is warranted and caution should be used in patients with narrow-angle glaucoma. The anticholinergic component of Trelegy Ellipta, umeclidinium, should be used with caution in patients with urinary retention.

The beta<sub>2</sub>-agonist effects of vilanterol may have a cardiovascular effect (e.g., tachycardia, increased blood pressure, arrhythmias) or produce significant hypokalemia or hyperglycemia. Significant impact of Trelegy Ellipta may require discontinuation. Likewise, Trelegy Ellipta should be used cautiously in patients with coexisting conditions (e.g., diabetes, convulsive disorders, thyrotoxicosis, and those sensitive to sympathomimetic amines).

Trelegy Ellipta should be used cautiously with known strong CYP3A4 inhibitors.

## DRUG INTERACTIONS

Both fluticasone furoate and vilanterol are CYP3A4 substrates; Trelegy Ellipta should be used cautiously with known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, voriconazole).

As beta-agonists can potentiate the cardiovascular effects of monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), or other agents known to prolong the QT interval. Trelegy Ellipta should not be used within 2 weeks of these agents. Electrocardiographic changes and/or hypokalemia associated with non-potassium-sparing diuretics (e.g., loop or thiazide diuretics) can be acutely worsened by beta-agonists; use caution if Trelegy Ellipta is coadministered with one of these agents.

Beta-blockers should not routinely be used in patients using inhaled beta-agonists. If a beta-blocker must be used, it should be used with caution in patients using Trelegy Ellipta due to the risk of severe bronchospasm and contradicting pharmacology.

Avoid coadministration of Trelegy Ellipta with other anticholinergic-containing drugs due to the risk of additive adverse effects.

## COMMON ADVERSE EFFECTS

The most common adverse effects reported in key clinical trials with Trelegy Ellipta include headache (4%), back pain (4%), dysgeusia (2%), diarrhea (2%), cough (1%), oropharyngeal pain (1%), and gastroenteritis (1%).

## SPECIAL POPULATIONS

### Pregnancy

There are insufficient data on the use of Trelegy Ellipta or its components in pregnant women to inform a drug-associated risk.

### Pediatrics

The safety and efficacy of Trelegy Ellipta in patients  $\leq 18$  years old have not been established.

### Geriatrics

No dose adjustment of Trelegy Ellipta is required in geriatric patients; however, greater sensitivity in some older individuals cannot be ruled out.

### Hepatic or Renal Impairment

The safety and efficacy of Trelegy Ellipta in patients with hepatic or renal impairment have not been studied; however, limited data with individual components in patients with these conditions suggest no dosage adjustment is required.

## DOSAGES

Trelegy Ellipta is dosed as 1 inhalation once daily by the orally inhaled route at the same time each day. After administration, the patient should rinse his/her mouth to prevent oropharyngeal candidiasis.

## CLINICAL TRIALS<sup>2,3</sup>

*A literature search was performed using “fluticasone furoate, umeclidinium, and vilanterol” and “chronic obstructive pulmonary disease.”*

The efficacy of Trelegy Ellipta is based primarily on the coadministration of its components in 2 multicenter, randomized, double-blind, parallel-group, 12-week confirmatory trials (Trial 1, n=206; Trial 2, n=206). In both trials, patients were randomized to either umeclidinium and fluticasone furoate/vilanterol or placebo and fluticasone furoate/vilanterol. The primary endpoint was the change from baseline in trough (predose) forced expiratory volume in 1 second (FEV<sub>1</sub>) at day 85 (defined as the mean of the FEV<sub>1</sub> values obtained at 23 and 24 hours following the previous dose on day 84). Combined baseline demographics included a mean age of 64 years, 92% Caucasian, 66% male, an average smoking history of 48 pack-years, and 50% current smokers. At screening, the mean postbronchodilator percent predicted FEV<sub>1</sub> was 46% (range, 14 to 76) and the mean postbronchodilator FEV<sub>1</sub>/forced vital capacity (FVC) ratio was 0.48 (range, 0.21 to 0.7). In Trial 1, the addition of umeclidinium to fluticasone furoate/vilanterol demonstrated a statistically significant increase in mean trough FEV<sub>1</sub> versus placebo (124 mL; 95% confidence interval [CI], 93 to 154). In Trial 2, a similar result was found (mean trough FEV<sub>1</sub>, 122 mL; 95% CI, 91 to 152). Similar results were demonstrated for the secondary endpoint of the weighted mean FEV<sub>1</sub> (0 to 6 hours postdose) on day 84 in both trials (Trial 1: 153 mL [95% CI, 118 to 187]; Trial 2: 147 mL [95% CI, 114 to 179]). Less average rescue medication was used with the addition

of umeclidinium in both trials and a statistically significant difference was found in health-related quality of life (as measured by the St. George's Respiratory Questionnaire) in Trial 2 but not in Trial 1. The effect on exacerbations was not measured in clinical trials comparing the addition of umeclidinium or placebo to fluticasone furoate/vilanterol.

Notably, a higher dose of umeclidinium was also assessed in the clinical trial; however, a combination product containing this strength is not available.

## OTHER DRUGS USED FOR CONDITION<sup>4</sup>

Several other single agent and combination inhaled therapies are available for the treatment of COPD; however, Trelegy Ellipta marks the first triple therapy combination product approved for COPD.

Single-agent long-acting inhaled antimuscarinics (LAMAs) approved for COPD include aclidinium bromide (Tudorza<sup>®</sup> Pressair<sup>®</sup>), glycopyrrolate (Seebri<sup>®</sup> Neohaler<sup>®</sup>), tiotropium (Spiriva<sup>®</sup> HandiHaler<sup>®</sup>, Spiriva Respimat<sup>®</sup>), and umeclidinium (Incruse<sup>®</sup> Ellipta<sup>®</sup>).

Single-agent inhaled LABAs approved for COPD include arformoterol (Brovana<sup>®</sup>), formoterol (Foradil<sup>®</sup> Aerolizer<sup>®</sup>, Perforomist<sup>®</sup>), indacaterol (Arcapta<sup>®</sup> Neohaler), olodaterol (Striverdi<sup>®</sup> Respimat), and salmeterol (Serevent<sup>®</sup> Diskus<sup>®</sup>).

LABA/LAMA inhaled combination products approved for COPD include formoterol/glycopyrrolate (Bevespi Aerosphere<sup>®</sup>), indacaterol/glycopyrrolate (Utibron<sup>®</sup> Neohaler), tiotropium/olodaterol (Stiolto<sup>®</sup> Respimat), and umeclidinium/vilanterol (Anoro<sup>®</sup> Ellipta).

ICS/LABA inhaled combinations products approved for COPD include budesonide/formoterol (Symbicort<sup>®</sup>), fluticasone furoate/vilanterol (Breo<sup>®</sup> Ellipta), and fluticasone propionate/salmeterol (Advair<sup>®</sup> Diskus).

Short acting inhaled bronchodilators and select oral agents, including theophylline and phosphodiesterase-4 inhibitors, are also approved for COPD.

## PLACE IN THERAPY<sup>5,6,7,8</sup>

The 2017 updated Global Initiative for Chronic Obstructive Lung Disease (GOLD) Global Strategy for the Diagnosis, Management, and Prevention of COPD guidelines classify patients separately by *both* their GOLD severity (airflow limitation range, 1 to 4 with increasing severity) *and* exacerbation/symptom assessment (exacerbation risk and symptoms range, A to D with increasing risk) (e.g., GOLD grade 4, group D). The guidelines recommend treatment plans for COPD based on the aforementioned patient group categories, identified by disease severity (airflow limitation), symptoms, comorbidities and exacerbation/hospitalization risk, although all treatment should be individualized. There is some evidence for use of triple therapy (ICS plus LABA plus LAMA) for Group D patients, if dual therapy is insufficient.

The 2011 American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society (ACP/ACCP/ATS/ERS) guidelines state combination therapy with an inhaled LABA, LAMA, or ICS may be used in lieu of monotherapy for patients with FEV<sub>1</sub> < 60%; however, the consensus group has offered this as a weak recommendation due to moderate quality evidence. Further, the guidelines suggest there is no clear outline for which patients would benefit the most from combination therapy over monotherapy. A 2015 joint guideline from the ACCP and the Canadian Thoracic Society (CTS) also recommends treatments based on data from published trials on

decreased acute exacerbations of COPD. While the guidelines do not specifically recommend triple therapy, they do state that a stepwise approach is reasonable and triple therapy may be appropriate in select patients with the impact assessed independently. The 2017 joint guidelines from ERS/ATS on the preventions of COPD exacerbations do not make a recommendation regarding triple therapy.

Trelegy Ellipta marks the first triple therapy combination product approved for COPD and offers an additional treatment option for patients with severe COPD who are not adequately managed with guideline-recommended dual therapy.

## SUGGESTED UTILIZATION MANAGEMENT

<b>Anticipated Therapeutic Class Review (TCR) Placement</b>	Glucocorticoids, Inhaled
<b>Clinical Edit</b>	<p><b>Initial:</b> Patient must meet the following criteria for approval:</p> <ul style="list-style-type: none"> <li>▪ Patient age <math>\geq</math> 18 years; AND</li> <li>▪ Diagnosis of chronic obstructive pulmonary disease (COPD); AND</li> <li>▪ Trial and failure (as defined by continued symptoms, including exacerbations) of adequate treatment with 2 dual combination therapies (e.g., inhaled corticosteroid plus long-acting beta-agonist or long-acting beta-agonist plus long-acting antimuscarinic); AND</li> <li>▪ Patient does not have known hypersensitivity to milk proteins, fluticasone, umeclidinium, vilanterol, or other known excipients.</li> </ul> <p><b>Renewal:</b> Patient must meet the following criteria for approval:</p> <ul style="list-style-type: none"> <li>▪ Patient continues to meet criteria defined for initial approval; AND</li> <li>▪ Documentation of continued efficacy via prescribers expert opinion on patient evaluation; AND</li> <li>▪ Patient has not experienced any intolerable adverse effects (e.g., hypersensitivity, bronchospasm, worsening of intraocular pressure, increased severe infections).</li> </ul>
<b>Quantity Limit</b>	One inhaler (30 blister strips)/30 days
<b>Duration of Approval</b>	12 months
<b>Drug to Disease Hard Edit</b>	None

## REFERENCES

- 1 Trelegy Ellipta [package insert]. Research Triangle Park, NC; GlaxoSmithKline; September 2017.
- 2 Trelegy Ellipta [package insert]. Research Triangle Park, NC; GlaxoSmithKline; September 2017.
- 3 Siler TM, Kerwin E, Sousa AR, et al. Efficacy and safety of umeclidinium added to fluticasone furoate/vilanterol in chronic obstructive pulmonary disease: results of two randomized studies. *Respir Med.* 2015; 109(9): 1155-1163. DOI: 10.1016/j.rmed.2015.06.006.
- 4 Clinical Pharmacology. Available at: <http://www.clinicalpharmacology-ip.com/default.aspx>. Accessed October 23, 2017.
- 5 Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) Updated 2017. Available at: <http://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/>. Accessed October 23, 2017.
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- 7 Criner GJ, Bourbeau J, Diekemper RL, et al. Prevention of acute exacerbations of COPD: American College of Chest Physicians and Canadian Thoracic Society guideline. *Chest*; 2015; 147(4): 894-942. DOI: 10.1378/chest.14-1676. Available at: <http://www.chestnet.org/Guidelines-and-Resources>. Accessed October 23, 2017.

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8 Wedzicha JA, Calverley PMA, Albert RK, et al. Prevention of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. Eur Respir J. 2017; 50(3): DOI: 10.1183/13993003.02265-2016. Available at: <https://www.thoracic.org/statements/>. Accessed October 23, 2017.